

II. REMARKS

A. Status of the Claims

Claims 1, 5-27, and 30-32 were pending in the case at the time of the Office Action, with claims 16-26 and 31-32 having been previously withdrawn from consideration. Claims 1 and 27 have been amended in the Amendment set forth herein. Claims 2-4 and 28-29 have been canceled without prejudice or disclaimer. No new claims have been added. Support for the amendments of claims 1 and 27 can be found generally throughout the specification, such as in the claims as originally filed and page 3, line 28 – page 4, line 2. Thus, claims 1, 5-15, 27, and 30 are currently under consideration.

B. The Rejections Under 35 U.S.C. §103(a) Are Overcome

1. Rejections Based on Naughton in View of Mitchell, Patel, and Wolff

Claims 1, 5, 8-15, 27, and 35 are rejected under 35 U.S.C. §103(a) as being unpatentable over Naughton (U.S. Patent 5,830,708) in view of Mitchell *et al.* (U.S. Patent App. Pub. No. 2002/0115208; hereinafter “Mitchell”), Patel *et al.* (U.S. Patent 7,087,089; hereinafter “Patel”) and Wolff *et al.* (WO 99/55379; hereinafter “Wolff”). The Examiner argues that it would have been obvious for an ordinary skilled artisan to modify the method of Naughton by preparing a decellularized bone marrow extracellular matrix material harvested from the bone marrow of a donor animal, including a human donor, whose parenchymal cells of the bone marrow have been transfected with a polynucleotide encoding a protein of interest in light of the teachings of Mitchell, Patel, and Wolff. Applicants respectfully traverse.

a. The Legal Standard

A finding of obviousness requires that “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been

obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. §103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467; *see also*, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Federal Register, Vol. 72, No. 195, October 10, 2007, pages 57527-57528. The Supreme Court also stated that it is “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the ways the claimed new invention does” *KSR*, 127 S.Ct. at 1741, 82 U.S.P.Q.2d at 1396.

In rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). In setting forth a *prima facie* case of obviousness, it is necessary to show “some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR*, 127 S.Ct. 1727 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). The Examiner has failed to establish a *prima facie* case of obviousness for the following reasons:

b. The References Cited by the Examiner Fail to Teach or Suggest Conducting Steps (a) and (b) of Independent Claims 1 and 35 Prior to Harvesting Step (c)

Step (a) of independent claims 1 and 27 (the only independent claims under consideration) recites “conditioning body tissue of a donor animal *in vivo* to produce the biological material in an amount different than the amount of the biological material that the body tissue would produce absent the conditioning.” Step (b) of independent claims 1 and 27 recites “allowing the conditioned body tissue to produce the biological material *in vivo*.” Step c of independent claims 1 and 27 recites “decellularizing the conditioned body tissue to obtain the extracellular matrix material containing the biological material.”

i. Naughton

Naughton does not teach step (a) at all. Naughton is directed to *in vitro* cell culture techniques, and not *in vivo* techniques. Specifically, Naughton concerns a method for culturing extracellular matrix-secreting human stromal cells on a biocompatible three-dimensional framework *in vitro*. Abstract and col. 4, lines 6-18 (emphasis added). “The extracellular matrix proteins are derived from a living stromal tissue prepared *in vitro* by growing stromal tissue on a three dimensional framework resulting in a multi-layer cell culture system.” Col. 5, lines 26-32 (emphasis added). Naughton does not teach or suggest conditioning cells *in vivo*.

While col. 10, lines 61-68 recites that “it may be desirable to prepare an extracellular matrix containing a foreign gene product” and that “the cells may be genetically engineered to express the gene product” it does not teach or suggest genetically engineering such cells *in vivo*. In view of Naughton’s focus on *in vitro* culturing of cells, at most this section of Naughton may suggest *in vitro* genetic engineering of cultured cells. The Examiner has not cited, nor do

Applicants identify, any information in Naughton that amounts to a suggestion to condition cells to express a foreign gene *in vivo*.

Because Naughton does not teach or suggest step (a), it follows that it does not teach or suggest step (b), which concerns allowing the conditioned body tissue to produce the biological material *in vivo*. Thus, Naughton fails to provide any teaching or suggestion to provide for either of steps (a) or (b) of independent claims 1 and 35, or of any of the remaining claims cited which depend from these claims.

ii. Mitchell

Mitchell does not teach step (a) of conditioning body tissue of a donor animal *in vivo* to produce the biological material in an amount different than the amount of the biological material that the body tissue would produce absent the conditioning. The Examiner cites to Mitchell as teaching that “tissue engineered constructs produced at least in part by culturing the tissue in vivo are also contemplated.” Office Action, page 5, citing to Mitchell para [067]. However, the term “tissue engineered constructs” as used in Mitchell does not concern genetic engineering of cells to express a foreign protein. Rather, Mitchell defines “tissue engineered construct” to refer to “a two or three dimensional mass of living mammalian tissue produced primarily by growth in vitro” or “at least in part by growth in vivo on an artificial substrate.” Para [0052]. Further, the Examiner’s citation to para [096] does not amount to a teaching or suggestion to genetically engineer cells.

Because Mitchell does not teach or suggest step (a) as to conditioning via genetic engineering, it follows that it does not teach or suggest step (b) of allowing the conditioned body

tissue to produce the biological material *in vivo*. Further, as to other methods of conditioning, Mitchell does not teach or suggest conducting steps (a) and (b) prior to harvesting steps (c).

iii. Patel

Patel does not teach or suggest step (a) of conditioning body tissue of a donor animal *in vivo* to produce the biological material in an amount different than the amount of the biological material that the body tissue would produce absent the conditioning. The Examiner's citation to use of transgenic animals as a pre-conditioned donor animal does not amount to a teaching or suggestion to provide for conditioning *in vivo*. See Office Action, paragraph bridging pages 5-6. The Examiner has not set forth any evidence that an *in vivo* conditioning technique is performed on such an animal.

Further, even if use of transgenic animals was for some reason considered to be *in vivo* genetic engineering, there is no teaching or suggestion in Patel to indicate that the conditioning resulted in production of a biological material in an amount different than the amount of the biological material that the body tissue would produce absent the conditioning. Rather, Patel, in discussing transgenic animals, makes reference to an example of animals such as pigs raised for "meat production" and certainly no information to suggest production of VEGF (the elected species) as the biological material or any other biological agent.

Because Patel does not teach or suggest step (a), it follows that it does not teach or suggest step (b) of allowing the conditioned body tissue to produce the biological material *in vivo*. Thus, Patel fails to provide any teaching or suggestion to provide for either of steps (a) or (b) of independent claims 1 and 35.

Further, Patel does not teach or suggest that said conditioned body tissue is the tissue which is harvested and decellularized, as required by the presently pending method claims.

iv. *Wolff*

Wolff does not teach or suggest conducting steps (a) and (b) of independent claims 1, and does not teach a harvesting step (c). While Wolff discusses delivering a polynucleotide into certain parenchymal cells of a mammal, the Examiner has not established that it teaches or suggests step (c) of harvesting conditioned tissue, nor has the Examiner established that it teaches or suggests performing any harvesting step following a conditioning step.

Thus, because the Examiner has failed to establish that the cited combination of references teaches or suggests each limitation of the claimed invention, including conducting steps (a) and (b) prior to step (c), there can be no *prima facie* case of obviousness.

c. *One of Ordinary Skill in the Art Would Not be Motivated to Combine Reference Teachings to Lead to the Claimed Invention*

As discussed above, Naughton does not teach or suggest the conditioning step (a) of the present invention – *i.e.*, conditioning body tissue of a donor animal *in vivo* to produce the biological material in an amount different than the amount of the biological material that the body tissue would produce absent the conditioning. As discussed above, Naughton is directed to culturing cells on a biocompatible framework *in vitro*. See abstract. While col. 10, lines 61-68 recites that “it may be desirable to prepare an extracellular matrix containing a foreign gene product” and that “the cells may be genetically engineered to express the gene product” it does not teach or suggest genetically engineering such cells *in vivo*. In view of Naughton’s emphasis on *in vitro* culturing of cells, there is nothing in Naughton that amounts to a suggestion to condition cells to express a foreign gene *in vivo*. Nor does Naughton teach or suggest a

conditioning step that occurs prior to the step of harvesting the conditioned body tissue from the donor animal and decellularizing the conditioned body tissue.

Mitchell does not provide the missing motivation to provide for *in vivo* conditioning (genetic engineering) of cells. As discussed above, the Examiner, arguing that Mitchell provides motivation for *in vivo* conditioning, cites to Mitchell as teaching that “tissue engineered constructs produced at least in part by culturing the tissue *in vivo* are also contemplated” Office Action, page 5, citing to Mitchell para [067]. However, the term “tissue engineered constructs” as used in Mitchell does not concern genetic engineering of cells to express a foreign protein. Rather, Mitchell defines “tissue engineered construct” to refer to “a two or three dimensional mass of living mammalian tissue produced primarily by growth *in vitro*” or “at least in part by growth *in vivo* on an artificial substrate.” Para [0052]. Thus, Mitchell’s tissue engineered constructs produced at least in part by culturing cells *in vivo* does not concern genetic engineering of cells, but rather pertains to growth *in vivo* on an artificial substrate. The Examiner is reminded that the elected species of conditioning is genetic engineering, and the Examiner has not cited any information in Mitchell to provide for motivation to genetically engineer cells *in vivo*.

The Examiner’s citation to paragraph [096] of Mitchell concerning exposing developing tissue engineered constructs to certain stimuli is not dispositive in showing *in vivo* conditioning as to the elected species of genetic engineering. Thus, neither Mitchell nor Naughton concern an *in vivo* conditioning that corresponds to the elected species of genetic engineering.

Further, even if such a step was taught in Mitchell, one of ordinary skill in the field would not necessarily be motivated to modify Naughton to provide for an *in vivo* conditioning

step. Both Mitchell and Naughton teach the criticality of growing cells *in vitro*. See abstracts of both references. To the extent that one of ordinary skill in the art might have been motivated to genetically engineer cells, it would make sense for such modification to occur *in vitro*, and not *in vivo*.

To the extent that Mitchell teaches any step that could be construed as a conditioning step, it teaches exposure of developing tissue to certain stimuli, and such exposure occurs after the body tissue is harvested. However, this sequence of exposure followed by conditioning is contrary to the sequence recited in the method of claims 1 and 27.

Patel does not provide the missing suggestion or motivation to lead to the claimed invention. The Examiner's citation to use of transgenic animals as a pre-conditioned donor animal does not amount to a teaching or suggestion to provide for conditioning *in vivo*. See Office Action, paragraph bridging pages 5-6, citing to col. 3, lines 11-21. Further, even if use of transgenic animals was considered to be *in vivo* genetic engineering, there is no teaching or suggestion in Patel to indicate that the conditioning resulted in production of a biological material in an amount different than the amount of the biological material that the body tissue would produce absent the conditioning. Rather, Patel, in discussing transgenic animals, makes reference to an example of animals such as *pigs* raised for *meat production* and provides no motivation to modify the teachings of any of the previous references to provide for the production of VEGF (the elected species) or any other therapeutic agent in a donor human. Again the Examiner is reminded that the species of donor animal that has been elected is human, and application of a technique to transgenic pigs modified for meat production does not amount to a suggestion or motivation to provide for genetic engineering of human cells to express a biological agent such as VEGF *in vivo*. Patel simply does not provide the missing suggestion

or motivation to modify the teachings of the other cited references to lead to the claimed invention.

Furthermore, the Examiner is reminded that the elected species is a human. The section of Patel concerning transgenic animals and pigs raised for “meat production” does not amount to a teaching or suggestion for genetically engineering human tissue to produce a therapeutic agent, such as VEGF.

While Wolff is cited as disclosing a process for delivering a polynucleotide encoding a protein of interest into parenchymal cells within tissues *in situ* or *in vivo*, it does not teach or suggest a method for production of a secreted extracellular matrix. It does not provide any suggestion or motivation to modify the teachings of Naughton or Mitchell because both Naughton and Mitchell include culturing extracellular matrix-secreting cells *in vitro* as an important aspect of the invention. The Examiner has not cited any specific information in Wolff that would lead a person of ordinary skill in the art to modify a key aspect of Naughton and Mitchell to provide for *in vivo* genetic engineering of cells, particularly when both references teach the feasibility of *in vitro* culturing of cells to produce extracellular matrix. The Examiner has not presented any reasonable expectation for success of such a modification of the method of Naughton or Mitchell. Wolff does not concern any method for production of extracellular matrix. Furthermore, there is no reasonable expectation of success that such a modification of Naughton and Mitchell would result in successful delivery of a polynucleotide into bone marrow. Wolff provides no data setting forth delivery of a polynucleotide into bone marrow.

In addition, one of ordinary skill in the art would not be motivated to combine the teachings of any of references cited by the Examiner. Each employs different body tissues

and/or different techniques to achieve the desired objectives. Wolff explicitly states that parenchymal cells are different from cells of the connective tissue and exclude fibroblasts (see page 7, lines 16-20), and thus teaches away from the stromal cells of Naughton. Based on the teachings of Wolff, a person of ordinary skill in the art would reasonably expect stromal cells and parenchymal cells to be structurally and functionally different and would each require a different approach for conditioning and culturing. Thus, the person of ordinary skill in the art would have no motivation to apply the delivery process of Wolff to the stromal cells used in the methods of Naughton.

Applicants submit that the teaching of Naughton is complete for its intended purpose and thus, a person of ordinary skill in the art would have no motivation to use any additional references, let alone three secondary references (*i.e.*, Mitchell, Patel, and Wolff) to modify the teachings of Naughton. *In re Herschler*, 591 F.2d 693, 200 U.S.P.Q. 711 (C.C.P.A. 1979). In *In re Herschler*, the applicant taught the use of dimethyl sulfoxide (DMSO) to enhance transdermal penetration of a number of compounds, and claimed the process of applying to the skin a mixture comprising DMSO and a physiologically active steroid. 591 F.2d at 695, 200 U.S.P.Q. at 712. The Board rejected the claims as obvious over a primary reference (the Lubowe patent), which disclosed a hair lotion containing an estrogenic hormone and a solubilizing agent other than DMSO, combined with a secondary reference (Faust), which taught that DMSO is a safe and effective solubilizing agent for cosmetic or dermatologic use. The CCPA reversed the Board's rejection on the grounds that disclosure of the primary reference was already complete for its intended purpose, so that one of ordinary skill in the art would not have been motivated to use the DMSO of the secondary reference.

Similar to the Lubowe patent, the disclosure of Naughton is complete for its intended purpose, namely culturing extracellular matrix-secreting human stromal cells on a biocompatible three-dimensional framework in vitro. None of Mitchell, Patel, and Wolff provide any suggestion or motivation to modify Naughton to provide for in vivo genetic engineering.

The Examiner appears to be using hindsight reconstruction to pick and choose from among the disclosures of the references to arrive at the presently claimed invention. This is improper when one of ordinary skill in the art would have no reason to combine the teachings of the references. See *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988). The Supreme Court in *KSR* stated that it is “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the new invention does” 127 S.Ct. at 1741.

The foregoing analysis set forth by Applicants takes into consideration the totality of the teachings of Naughton, Mitchell, Patel, and Wolff. Applicants have considered each of the references separately to demonstrate that they do not teach or suggest teach limitation of the claimed invention, and have considered each of the references together to demonstrate that together there is no suggestion or motivation to lead to the claimed invention or any reasonable expectation of success to practice the claimed invention based on the teaching of these references.

For the foregoing reasons, Applicants submit that a *prima facie* case of obviousness cannot be established based on the cited references. Withdrawal of the rejection of claims 1, 5, 8-15, 27, and 35 under 35 U.S.C. §103(a) as respectfully requested.

2. Rejections Based on Naughton in View of Mitchell, Patel, and Wolff, and Further in View of Herlyn

Claims 13 and 30 are rejected under 35 U.S.C. §103(a) as being unpatentable over Naughton in view of Mitchell, Patel, and Wolff as applied above, and further in view of Herlyn *et al.* (WO 98/39035; hereinafter “Herlyn”) for reasons previously of record. Herlyn is cited as teaching that VEGF is useful in Wound repair in mammalian tissue by enhancing fibroblast growth and formation into a matrix, enhancing keratinocyte growth and angiogenesis and ex vivo method for infecting tissue to be transplanted with a recombinant virus expressing VEGF prior to transplantation. The Examiner argues that it would have been obvious for an ordinary artisan to further modify the combined method of Naughton, Mitchell, Patel, and Wolff by selecting VEGF as a foreign gene product to be incorporated into the decellularized extracellular matrix in light of the teachings of Herlyn. Applicants respectfully traverse.

As discussed in Applicants’ previous response to Office Action, Herlyn discloses a method for repairing defects and inducing vascularization in mammalian tissue by administering to the tissue a recombinant replication defective virus carrying a selected growth factor gene under operative control of regulatory sequences which direct the expression of the growth factor (see abstract). Herlyn fails to remedy the deficiencies of Naughton, Mitchell, Patel, and Wolff because Herlyn does not teach or suggest performing a conditioning step (genetic engineering) of donor human in vivo prior to harvesting the conditioned body tissue from the human. Further, Herlyn does not appear to concern any method for producing decellularized extracellular matrix material.

The Examiner appears to be using hindsight reconstruction to pick and choose from among the disclosures of the references to arrive at the presently claimed invention. This is improper as discussed above. See *In re Fine*, 837 F.2d at 1075.

In view of the foregoing, Applicants submit that a *prima facie* case of obviousness cannot be established based on the cited references. Withdrawal of the rejection of claims 13 and 35 under 35 U.S.C. §103(a) based on Naughton, Mitchell, Patel, Wolff, and Herlyn is respectfully requested.

3. Rejections Based on Naughton in View of Mitchell, Patel, and Wolff, and Further in View of Schwarz

Claims 6 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over Naughton in view of Mitchell, Patel, and Wolff as applied above, and further in view of Schwarz *et al.* (U.S. 6,656,916; hereinafter “Schwarz”) for reasons previously of record. Schwarz is cited as teaching administering to a donor animal a therapeutic agent (glucocorticoid) to a body tissue prior to or after delivery of a gene. The Examiner argues that it would have been obvious for an ordinary skilled artisan to further modify the teachings of Naughton, Mitchell, Patel, and Wolff by also administering to the donor animal a therapeutic agent such as a glucocorticoid to a body tissue prior to or after delivery of a gene to lead to the claimed invention. Applicants respectfully traverse.

Schwarz fails to remedy the deficiencies of Naughton, Mitchell, Patel, and Wolff because Schwarz does not teach or suggest performing a conditioning step (genetic engineering) of donor human *in vivo* prior to harvesting the conditioned body tissue from the human. Further, Schwarz does not appear to concern any method for producing decellularized extracellular matrix material.

As with the previous rejections, the Examiner appears to be using hindsight reconstruction to pick and choose from among the disclosures of the references to arrive at the presently claimed invention. This is improper as discussed above. See *In re Fine*, 837 F.2d at 1075.

In view of the foregoing, Applicants submit that a *prima facie* case of obviousness cannot be established based on the cited references. Withdrawal of the rejection of claims 6-7 under 35 U.S.C. §103(a) based on Naughton, Mitchell, Patel, Wolff, and Schwarz is respectfully requested.

C. Conclusion

In view of the foregoing, it is respectfully submitted that each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Monica A. De La Paz
Reg. No. 54,662
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
512.474.5201 (telephone)
512.536.4598 (fax)

Date: November 13, 2008